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Signed Andrew Gerry

Dated 25 November 2003

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26SEP02 E751042-1 C58534
P01/7700 0.00-0222291.7

1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference JDH/JA/2557GB

2. Patent application number *(The Patent Office will fill in this part)* 0222291.7 26 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Smith & Nephew, plc
15 Adam Street
LONDON WC2N 6LA

3969284006

Patents ADP number *(if you know it)* ~~03969284001~~

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention

ADHESIVE BONE CEMENT

5. Name of your agent *(if you have one)*

JOHN HOBBS

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Smith & Nephew Group Research Centre
York Science Park, Heslington,
YORK YO10 5DF
United Kingdom

Patents ADP number *(if you know it)* 6134959001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	5 ✓
Claim *(s)*	CF
Abstract	
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 24/09/02

JOHN HOBBS

12. Name and daytime telephone number of person to contact in the United Kingdom

John Hobbs 01904 824050

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

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d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

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ADHESIVE BONE CEMENT

The invention relates to bone adhesives and bone cements, in particular the use of novel adhesive bone cements in surgery.

There is a clinical need to fill holes in bone, for example following removal of diseased bone or following loss of osteoporotic bone; or for the fixation of devices into bone, for example artificial hip stem fixation. These defects can be repaired using ceramic bone grafts, or more preferably using bone cements that can be moulded before setting.

The most widely used bone cements are based on polymethylmethacrylate (PMMA). These have good strength characteristics but also have a number of drawbacks: they are not adhesive to bone and release heat on curing.

Consequently ceramic bone cements have been created based on the dissolution of tetracalcium phosphate and dicalcium phosphate dihydrate (ceramic cements). These have been formed with a variety of other soluble precursors to yield cements with altered biological properties. One such cement, developed by reacting at a lower pH, is called brushite cement. This ceramic cement is capable of being replaced by bone following implantation. However, this improvement in biocompatibility is coupled with poorer mechanical properties. Currently used ceramic bone cements such as brushite are brittle and may crack and delaminate from the bone surface when put under load.

The problem of bone cement brittleness has been tackled by the addition of retarding agents such as calcium sulphate hemihydrate (15% by weight) or calcium pyrophosphate (5% by weight) that increases the diametrical tensile strength of the cement three-fold to ~3MPa by inhibiting calcium orthophosphate crystallisation. However, this is still below the tensile strength levels required for bone cement under load. Furthermore there have been no solutions proposed for improving the lamination strength of bone cements.

There are other clinical needs that are not met by current products. For example, during reconstructive surgery it is sometimes desirable to attach together a number of bone fragments. This is not possible using currently available, non-adhesive bone cements (PMMA or ceramic).

There exists a range of adhesive methodologies that could be used to stick bone cements and fragments in place. These include biological glues such as fibrin (the polymerisation of fibrinogen to fibrin via thrombin catalysis) and synthetic glues such as cyanoacrylates. It is also possible to surgically join bones by the use of metal pins, screws and plates. However, none of these approaches adequately solves the problem.

Fixing the bone cement or fragments in place with a biological adhesive is not an appropriate solution because these glues do not have sufficient strength to cope with the stresses within bone.

Fixing the bone cement or fragments in place with a standard synthetic adhesive is not an appropriate solution because many synthetic adhesives have been manufactured for industrial and consumer uses so are not suitable for use in the body due to toxicity of adhesive ingredients, slow adhesive curing in moist conditions at body temperature and poor biodegradation of the cured adhesive.

Fixing the bone cement or bone fragments into place with metal pins, although a commonly used technique, is not an optimal solution as this causes considerably more trauma to the site and the patient.

It is an objective of the present invention to provide biocompatible, ceramic-based bone cement with appropriate strength characteristics that is adhesive that sets over a clinically relevant timescale (1 to 30 minutes at room temperature).

Accordingly, to the present invention there is provided a bone cement composition comprising a calcium component (for example β tricalcium phosphate) and an aqueous solution of polyphosphoric acid.

The polyphosphoric acid solution may comprise a mixture of pyrophosphoric acid and orthophosphoric acid.

Typically the aqueous solution of polyphosphoric acid will comprise between 5 and 90% water by weight.

Typically the aqueous solution of polyphosphoric acid will comprise at least 10% pyrophosphoric acid by weight

Preferably the aqueous solution of polyphosphoric acid will comprise no more than 85% pyrophosphoric acid by weight

Typically the aqueous solution of polyphosphoric acid will comprise at least 5% orthophosphoric acid by weight.

Preferably the aqueous solution of polyphosphoric acid will comprise no more than 85% orthophosphoric acid by weight

Typically the cement will comprise between 0.8g to 3.5g calcium component to 1ml polyphosphoric acid solution.

Preferably the calcium component will be a solid in the 10nm to 100μm size range.

Aptly the calcium component will be a calcium phosphate.

Typically the calcium component will be β tricalcium phosphate (β-TCP), α-tricalcium phosphate (α-TCP), tetracalcium phosphate (TTCP), dicalcium phosphate anhydrous (DCPA), dicalcium phosphate dihydrate (DCPD) or calcium oxide (CaO).

Preferably, the adhesion properties of the cement are conferred by the polyphosphoric acid solution component of the cement where said solution comprises water within the range 0 to 90% by weight, pyrophosphoric acid 5 to 80% by weight and orthophosphoric acid 5 to 80% by weight.

Preferably, the strength properties of the cement are conferred by the polyphosphoric acid solution component of the cement where said solution comprises water within the range 30 to 80% by weight, pyrophosphoric acid 5 to 50% by weight and orthophosphoric acid 5 to 40% by weight.

Preferably, the setting properties of the cement are conferred by the polyphosphoric acid solution component of the cement where said solution comprises water within the range 45 to 90% by weight, pyrophosphoric acid 5 to 55% by weight and orthophosphoric acid 5 to 40% by weight.

A cement that combined preferable adhesive, strength and setting properties would preferably contain polyphosphoric acid solution comprising water within the range 45 to 80% by weight, pyrophosphoric acid 5 to 50% by weight and orthophosphoric acid 5 to 40% by weight.

Example 1

Three different adhesive bone cements were made by mixing βTCP (1.5 g/ml) and aqueous polyphosphoric acid solution components as shown in Table 1. The adhesive tensile strength, compressive strength and setting times for each cement are shown below in Table 1.

Liquid component (Wt%)			Adhesive tensile strength (MPa) *(a)*	Compressive strength (MPa) *(b)*	Initial setting time (Min) *(c)*	Final setting time (Min) *(c)*
Water	Pyrophosphoric acid	Orthophosphoric acid				
55	36	9	0.5	10.1	13.5	22.2
57	30	13	1.4	8.0	8.0	26.0
66	8	26	0.4	4.1	18.3	30.0

Table 1. Characteristics of three different adhesive bone cements.

a) *Adhesive tensile strength measured by bonding together defatted ovine femurs and making tensile strength measurements after 3 hours*

b) *Compressive strength was measured on small set cylinders of adhesive*

c) *Setting time was measured using the Gilmore needle method*